FULL TEXT OF CASES (USPQ FIRST SERIES)
Cross et al. v. Iizuka et al., 224 USPQ 739 (CA FC 1985)

Cross et al. v. Iizuka et al.

(CA FC)
224 USPQ 739

Decided Jan. 28, 1985
No. 84-1111
U.S. Court of Appeals Federal Circuit

Headnotes

PATENTS

1. Patentability -- Utility (§ 51.75)

Board did not err in finding that in vitro utility disclosed in foreign priority application is sufficient to establish practical utility under 35 USC 101.

2. Patentability -- Utility (§ 51.75)

Rigorous correlation of pharmacological activity between disclosed in vitro utility and in vivo activity is not necessary where disclosure of pharmacological activity is reasonable based upon probative evidence.

3. Patentability -- Utility (§ 51.75)

35 USC 112 "how to use" requirement is satisfied, despite failure of disclosure to reveal dosages for novel compound per se, those skilled in art having had sufficient information at critical date to determine dosage for desired pharmacological activity.

Particular patents -- Imadazole Derivatives

Iizuka, et al., application, Imidazole Derivatives, award of priority over Cross et al., application, N-(Phenoxyalkyl) Imidazoles as Selective Inhibitors of the Thromboxane Synthetase Enzyme and Pharmaceutical Compositions Thereof, affirmed.

Case History and Disposition:

Appeal from Patent and Trademark Office Board of Patent Interferences.

Patent interference No. 100,650, between Peter E. Cross, et al., application, Serial No. 95,755, filed Nov. 19, 1979, and Kinji Iizuka, et al., application, Serial No. 68,365, filed Aug. 21, 1979. From decision awarding priority to party Iizuka, party Cross, et al. appeals. Affirmed.

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Judge:
Before Kashiwa, Bennett, and Bissell, Circuit Judges.

Opinion Text

Opinion By:
Kashiwa, Circuit Judge.

This appeal is from the decision of the United States Patent and Trademark Office (PTO) Board of Patent Interferences (Board) awarding priority on the single phantom count to Iizuka, et al. (Iizuka), the senior party. We affirm.

Background

Interference No. 100,650 was declared on 20 April 1981 between application serial No. 68,365, for "Imidazole Derivatives," filed by Iizuka on 21 August 1979 and application serial No. 95,755, for "N-(Phenoxyalkyl) Imidazoles as Selective Inhibitors of the Thromboxane Synthetase Enzyme and Pharmaceutical Compositions Thereof," filed by Cross, et al. (Cross) on 19 November 1979. The single phantom count of the interference is directed to imidazole derivative compounds and reads as follows:

> A compound selected from the group consisting of an imidazole derivative of the formula *Graphic material consisting of a chemical formula or diagram set at this point is not available. See text in hard copy or call BNA PLUS at 1-800-452-7773 or 202-452-4323.*
>
> wherein R is a hydrogen atom or an alkyl group having 1 to 6 carbon atoms, each of A_1 or A_2, which may be the same or different, are alkylene having 1 to 8 carbon atoms, m is 0 or 1, X is oxygen or sulfur, and each of R_1 or R_2, which may be the same or different, is a hydrogen atom *or an alkyl group having 1 to 6 carbon* atoms; R_3 is H, C_1-C_4 alkyl, C_1-C_4 alkoxy or halogen; and the pharmaceutically acceptable salts thereof. [1]

The applications of Cross and Iizuka both disclose inventions directed to imidazole derivative compounds which inhibit the synthesis of thromboxane synthetase, an enzyme which leads to the formation of thromboxane A_2 (TXA_2) [2] a highly unstable, biologically active compound which is converted to stable thromboxane B_2 by the addition of water. Thromboxane A_2, as of the time period during which the applications were filed, was postulated to be a causal factor in platelet

aggregation. [3] Platelet aggregation is associated with several deleterious conditions in mammalia, including humans, such as platelet thrombosis, pulmonary vasoconstriction or vasospasm, inflammation, hypertension, and collagen-induced thrombosis.

Pursuant to 37 C.F.R. §1.231(a)(4) each party moved to be accorded the benefit of a foreign priority application under 35 U.S.C. §119, Cross claiming priority based upon a British application filed 13 December 1978, and Iizuka claiming priority based upon a Japanese application filed 21 August 1978. Each party opposed the motion of the other party, each party contending that the other party's foreign priority application did not comply with the disclosure requirements of 35 U.S.C. §112.

The primary examiner granted each party's motion, noting that the utility alleged in each application was of a pharmacological nature, i.e., the inhibition of thromboxane synthetase, and that inasmuch as the single phantom count of the interference was directed to a compound, it was not necessary that utility be established by tests and dosages with respect to human beings. The examiner found that one of ordinary skill in the art would know how to use the imidazole derivatives, i.e., be able to determine specific dosages, for biological purposes. Based upon the filing dates of the foreign priority applications, [4] Iizuka was declared the senior party and a show cause order was issued against Cross.

Cross requested a final hearing on the issue of the sufficiency of the Japanese priority application of Iizuka, and moved for a testimony period to present evidence on this issue. A testimony period was granted over the opposition of Iizuka, and Cross took the testimony of his expert witness, Dr. Smith, and Iizuka took the testimony of his expert witness, Dr. Ramwell and also proferred several exhibits pursuant to 37 C.F.R. §1.282. All testimony and exhibits related to the sufficiency of Iizuka's Japanese priority application, i.e., whether it complied with the disclosure requirements of 35 U.S.C. §112.

Decision of the Board

The Board noted that the sole issue before it was whether Iizuka was entitled to the benefit of his Japanese priority application. [5] Relying on In re Bundy, 642 F.2d 430, 209 USPQ 48 (CCPA 1981), and Nelson v. Bowler, 626 F.2d 853, 206 USPQ 881 (CCPA 1980), the Board held that tests evidencing pharmacological activity may manifest a practical utility even though they may not establish a specific therapeutic use. The Board found that the Japanese priority application disclosed pharmacological activity in the similar activity of the imidazole derivatives of the count to imidazole and 1-methylimidazole, which possess an inhibitory action for thromboxane synthetase, and that practical utility was disclosed in the strong inhibitory action for thromboxane synthetase from human or bovine platelet microsomes, i.e., an in vitro utility. [6]

The Board further found that the Japanese priority application disclosed "how-to-use" knowledge directed to the practical utility in a microsome system, and that microsome assays were admittedly known in the art. A skilled worker could determine the relative strength of the imidazole compounds of the count vis-a-vis the known parent imidazole and 1-methylimidazole compounds for use in the microsome assay milieu. Knowledge of the pharmacological activities of compounds is beneficial to the medical profession, and requiring Iizuka to have disclosed in vivo dosages in the Japanese priority application would delay and frustrate researchers by failing to provide an incentive for early public disclosure of such compounds, thereby failing to further the public interest.

Accordingly, the Board held that the Japanese priority application contained an adequate how-to-use disclosure for the practical utility stated therein.

Issues

Whether the Board erred in finding that the utility disclosed in the Japanese priority application is sufficient to meet the practical utility requirement of 35 U.S.C. §101.

Whether the Board erred in finding that the Japanese priority application contained sufficient disclosure to satisfy the enablement, i.e., how-to-use, requirement of 35 U.S.C. §112. [7]

Opinion

Proper resolution of the issues before this court necessitates that we address, seriatim, the following questions: (1) What utility is disclosed by the Japanese priority application? (2) Does this stated utility comply with the "practical utility" requirement of 35 U.S.C. §101, as delimited by prior decisions of the judiciary? [8] (3) Does the Japanese priority application contain sufficient disclosure to meet the how-to-use requirement of §112 with respect to the stated utility?

It is axiomatic that an invention cannot be considered "useful," in the sense that a patent can be granted on it, unless substantial or practical utility for the invention has been discovered and disclosed where such utility would not be obvious. Brenner v. Manson, 383 U.S. 519, 148 USPQ 689 (1966). Where a constructive reduction to practice is involved, as contrasted to an actual reduction to practice, a practical utility for the invention is determined by reference to, and a factual analysis of, the disclosures of the application. Kawai v. Metlesics, 480 F.2d 880, 178 USPQ 158 (CCPA 1973).

1. Japanese Priority Application

The Board factually analyzed the Japanese priority application and found that the only effective disclosure relating to a stated utility for the imidazole derivative compounds of the phantom count was the following:

> [The compounds disclosed] are useful for treatment of inflammation, thrombus, hypertension, cerebral apoplexy, asthma, etc.
>
> Up to this time, it is a known fact that imidazole and 1-methylimidazole posses an inhibitory action for thromboxane synthetase and inhibit a biosynthesis of thromboxane A_2.
>
> (Prostaglandins, Vol. 13, pages 611-1977). However, since their inhibitory effect is not satisfactory one, these compounds have not been put to practical use yet as therapeutical medicines for diseases caused by thromboxane A_2, such as inflammation, hypertension, thrombus, cerebral apoplexy, asthma, etc.

> To develop some compounds possessing a strong inhibitory action for biosynthesis of thromboxane A_2, the present inventors devoted themselves to study for various imidazole derivatives, and as a result, found that the compounds [of this invention] possess a strong inhibitory action for
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>
> thromboxane synthetase from human or bovine platelet microsomes and are extremely useful as therapeutically active agents for diseases caused by thromboxane A_2, for example, inflammation, hypertension, thrombus, cerebal apoplexy, asthma, etc., and thus were proposed this invention based upon those findings.
>
> The imidazole derivatives * * * of this invention are novel compounds which are not described in literature, and which possess a strong inhibitory action for thromboxane synthetase from human or bovine platelet microsomes, and which exhibit a strong inhibitory action for biosynthesis of thromboxane A_2in mammalia including human. In general, a satisfactory inhibitory effect is found at a level of molar concentrations of 2.5 x 10 -8, for example, 2-[p-(1-imidazolylmethyl)phenoxy]-acetic acid hydrochloride produce the about 50% inhibitory effect at the molar concentrations of 2.5 x 10 -8. Accordingly, the imidazole derivatives of this invention are extremely useful as therapeutical medicines for diseases caused by thromboxane A_2, such as inflammation, hypertension, thrombus, cerebral apoplexy, asthma, etc.

The Board found that these pertinent sections of the Japanese priority application disclosed some activity or utility, namely that the imidazole derivative compounds of the count possess a strong inhibitory action for thromboxane synthetase in human or bovine platelet microsomes. Cross' position is that the stated purpose or *sole* comtemplated utility of the invention of Iizuka is to provide a novel class of compounds which provide "practical use" as "therapeutical medicines for diseases caused by thromboxane A_2," and therefore the Board erred in its finding as to the stated utility of the Japanese priority application.

While recognizing that Kawai constrains an applicant to entitlement to the benefit of only what is disclosed in the foreign priority application and no more, we also recognize that foreign priority applications, as subsequently filed in the PTO, typically have a style and format dissimilar to the arrangement of application elements suggested by 37 C.F.R. §1.77. In part this arises because of differences in filing requirements in foreign patent offices, and in part because of the awkwardness resulting from direct literal translations from a foreign language to English. Thus, while the factual determination of the stated utility in an application prepared in the United States may be relatively straightforward, [2]the factual analysis of a foreign priority application to determine the utility disclosed therein may be more laborious and open to varying interpretations.

The weakness of Cross' position is that a fair reading of the pertinent sections of the Japanese priority application as set forth above, discloses utility for the imidazole derivative compounds of the phantom count both as an inhibiting agent for thromboxan synthetase in human or bovine platelet microsomes, as found by the Board, and as therapeutically active agents preventing the biosynthesis of thromboxane A_2, thereby functioning as a medicine preventing deleterious conditions caused by thromboxane A_2, as contended by Cross.

Evidence of any utility is sufficient when the count does not recite any particular utility. Nelson v. Bowler, 626 F.2d 853, 856, 206 USPQ 881, 883 (CCPA 1980). See also Rey-Bellet v. Englehardt, 493 F.2d 1380, 181 USPQ 453 (CCPA 1974); Knapp v. Anderson, 477 F.2d 588, 177 USPQ 688 (CCPA 1973); Blicke v. Treves, 241 F.2d 718, 112 USPQ 472 (CCPA 1957). Here the Board, which is charged with the factual determination of utility, [10] has found that the specification of the Japanese priority application disclosed a utility for the imidazole derivative compounds of the phanton count in the inhibition of thromboxane synthetase in human or bovine platelet microsomes. Inasmuch as the Board is charged with making this factual determination when the issue is raised, inasmuch as they have so done in the instant case, and inasmuch as there is credible evidence to support this factual determination, we are not prepared to say that the Board erred in its

finding as to the stated utility disclosed in the Japanese priority application.

2. Practical Utility

As noted in the preceding part of this opinion, Cross has contended that the Board erred in its finding as to the utility disclosed in the Japanese priority application. This argument may be viewed in a different perspective, we believe, which is that the stated utility in the Japanese priority application, as found by the Board -- the inhibition of thromboxane synthetase in human or bovine platelet microsomes [11] -- is not sufficiently correlated to a pharmacological activity [12] to be a practical utility. In other words, Cross may be arguing that the minimum acceptable level of utility disclosed in an application claiming a compound having pharmacological activity must be directed to an in vivo utility in order to comply with the practical utility requirement of §101.

The starting point for a practical utility analysis is Brenner v. Manson, 383 U.S. 519, 148 USPQ 689 (1966). The Court in Brenner noted that "a simple, everyday word ["useful," as found in 35 U.S.C. §101] can be pregnant with ambiguity when applied to the facts of life." Id. at 529, 148 USPQ at 693. While noting that "one of the purposes of the patent system is to encourage dissemination of information concerning discoveries and inventions," id. at 533, 148 USPQ at 695, the Court found that a more compelling consideration in the determination of whether a patent should be granted "is the benefit derived by the public from an invention with substantial utility. Unless and until a process is refined and developed to this point -- where specific benefit exists in currently available form -- there is insufficient justification for permitting an applicant to engross what may prove to be a broad field." Id. at 534-35, 148 USPQ at 695. While we recognize that this case concerned a compound derived from a chemical process, we believe Brenner provides broad guidelines which are helpful in ascertaining what constitutes practical utility for compounds having a pharmacological effect.

In Nelson v. Bowley, 626 F.2d 853, 206 USPQ 881 (1980), our predecessor court, the Court of Customs and Patent Appeals, stated that "[k]nowledge of the pharmacological activity of any compound is obviously beneficial to the public" and concluded that "adequate proof of any such utility constitutes a showing of practical utility." Id. at 856, 206 USPQ at 883. [13] The tests [14] found by the court to be adequate proof of pharmacological activity or practical utility were a rat blood pressure (BP) test and a gerbil colon smooth muscle stimulation (GC-SMS) test. The BP test was an in vivo test, which was deemed by the court to be direct evidence as to the claimed activity, while the GC-SMS test was an in vitro test. [15]

The CCPA in Rey-Bellet v. Englehardt, 493 F.2d 1380, 1383, 181 USPQ 453, 454 (1974), stated that where a count contains no limitation related to utility, evidence establishing a substantial utility for any purpose is sufficient to show a reduction to practice. The court held that three in vivo tests [16] conducted in the United States prior to the filing of Englehardt's U.S. application failed to establish an actual reduction to practice. The court proceeded, however, to find sufficient evidence in the record to establish that Englehardt had conceived a utility for his compound prior to the filing date of his U.S. application. The evidence the court found to be sufficient was testimony by the inventor that he believed his compound would exhibit a particular pharmacological activity because of its structural similarity to anther compound which was known to possess the particular pharmacological activity. The court

found that the testimonial evidence of Englehardt was corroborated by two exhibits entered into evidence. The evidence adduced by Englehardt was found by the court to be sufficient proof that Englehardt had conceived that his compound had utility for the particular pharmacological activity prior to his U.S. filing date. The court further noted that this was a completed conception of utility because it appeared that nothing beyond the exercise of routine skill would have been required to demonstrate that Englehardt's compound possessed the particular pharmacological utility. While noting that the actual testing done was not sufficient to establish an actual reduction to practice, the court found that the extensive testing done in vivo on animals was routine in nature and was not, therefore, to be construed as an indicator that extensive research, i.e., inventive skill and/or undue experimentation, was required to resolve perplexing intricate difficulties related to the utilization of the compound for the particular pharmacological activity.

The CCPA in Kawai v. Metlesics, 480 F.2d 880, 178 USPQ 158 (1973), concurred with the finding of the Board that the applicants had failed to prove that their foreign priority application was adequate under the patent laws of the United States. The only disclosure in the foreign priority application relating to the compound of the count was that it exhibited "pharmacological effects on the central nervous system," which the applicants conceded was an inadequate disclosure. The applicants, however, relied upon a patent made of record as indicative of the general knowledge of one skilled in the art, which the applicants contended described a compound closely related to their claimed compound, to show utility or pharmacological activity for the compound of the count as an anticonvulsant. The court agreed with the board that there were sufficient structural dissimilarities between the compounds of the patent and those of the count to preclude reliance on the patent to supplement the disclosure deficiencies of the foreign priority application.

In Knapp v. Anderson, 477 F.2d 588, 177 USPQ 688 (CCPA 1973), the court, citing to Blicke v. Treves, 241 F.2d 718, 112 USPQ 472 (CCPA 1957), stated that "[i]t is well settled that if the counts do not specify any particular use, evidence proving substantial utility for any purpose is sufficient to establish an actual reduction to practice." Id. at 590, 177 USPQ at 690 (emphasis added). Noting that the only utility contemplated for the compounds of the count was as ashless dispersants in lubricant compositions used in internal combustion engines, the court found no error in the Board's holding that there was no actual reduction to practice because only a potential utility had been established, this holding based upon the Board's finding of a lack of correlation between bench tests and actual service conditions in a combustion engine.

The CCPA has held that nebulous expressions, such as "biological activity" or "biological properties," disclosed in a specification convey little explicit indication regarding the utility of a compound. In re Kirk 376 F.2d 936, 941, 153 USPQ 48, 52 (CCPA 1967). But, while agreeing with the Board that the specification failed to disclose a specific allegation of utility for any compound within the scope of the claims, and that reference in the specification to biological properties of the claimed compound was so general and vague as to be meaningless, the court implied that a disclosure in the specification that the requisite properties of the claimed compounds are similar to those of a natural or synthetic hormone of known activity may, in appropriate circumstances, supplement an application to rectify an inadequate disclosure relating to the practical utility for the compound. Id. at 942, 153 USPQ at 53.

Every utility question arising in an interference, in the final analysis, must be decided on the basis of its own unique factual circumstances. Relevant evidence must be judged as a whole for its persuasiveness in determining whether the suggested use for the compound of the count is a practical utility. Cf. Nelson, 626 F.2d at 858, 206 USPQ at 885.

The Board has found that the Japanese priority application of Iizuka disclosed a practical utility for the compounds of the phantom count in the inhibition of thromboxane synthetase in human or bovine platelet microsomes, i.e., an in vitro utility. Clearly, this stated utility as found by the Board has been delimited with sufficient specificity to satisfy the threshold requirements of Kawai and Kirk. The stated utility of the Japanese priority application is directed to a specific pharmacological activity possessed by the imidazole derivatives of the phantom count -- the inhibition of thromboxane synthetase in vitro. Thus, this court on review is not presented with a general allegation of "biological activity" or "biological properties" as was the CCPA in Kirk, nor is reliance on prior art required to ascertain what specific pharmacological activity the compound of the count possesses, the factual situation confronting the court in Kawai.

The Japanese priority application, moreover, disclosed that it was generally known in the art, as of the critical date, that the parent imidazole and 1-methylimidazole compounds possessed an inhibitory action for thrombox

ane synthetase. Reliance on this disclosure in the specification of the pharmacological property of the parent imidazole and 1-methylimidazole compounds, as going towards proof of the pharmacological activity of the imidazole derivatives of the phantom count, is particularly relevant in the instant case, we believe, because Iizuka is not relying on this inference to supplement an inadequate disclosure in the Japanese priority application regarding the pharmacological activity of the compound of the phantom count, but rather is relying on this inference as cumulative probative evidence showing an adequately disclosed practical utility in the Japanese priority application.

This court, in Rey-Bellet and Kawai, has implied that a particular pharmacological activity identified with prior art compounds may have probative value as to the fact that the compound of the count possesses this particular pharmacological activity where there is a structural similarity between the prior art compounds and the compound of the count. Rey-Bellet, 493 F.2d at 1385-87, 181 USPQ at 456-58; Kawai, 480 F.2d at 890-91, 178 USPQ at 166-67. Cross has failed to proffer sufficient evidence or present any persuasive arguments going to the question of significant structural dissimilarities between the parent imidazole and 1-methylimidazole compounds and the imidazole derivatives of the phantom count. [17]

The expert of Iizuka, Dr. Ramwell, testified that, as of the critical date, there was an awareness on the part of those skilled in the art that the parent imidazole compound exhibited an inhibitory activity for thromboxane synthetase, in both in vitro and in vivo environments. Dr. Ramwell further testified that there was an awareness by those skilled in the art of a correlation between thromboxane A_2 and platelet aggregation, namely that thromboxane A_2 was a mediator in platelet aggregation. Several exhibits proferred by Iizuka corroborated Dr. Ramwell's testimony as to the general knowledge in the art with respect to the inhibitory effect of the parent imidazole compound for thromboxane synthetase. [18] Accordingly, the similar pharmacological activity of the parent imidazole and 1-methylimidazole compounds have probative value in the factual determination of practical utility for the compounds of the phantom count inasmuch as Cross has not met the burden of proof to establish structural dissimilarities between the parent imidazole and 1-methylimidazole compounds and the imidazole derivatives of the phantom count. Rey-Bellet, 493 F.2d at 1386-87, 181 USPQ at 457.

The Board found that there was adequate proof that the Japanese priority application disclosed a pharmacological activity for the compounds of the phantom count in inhibiting the action of thromboxane synthetase, similar to the pharmacological activity of the parent imidazole and 1-methylimidazole compounds which were found to possess an inhibitory action for thromboxane synthetase, this disclosed knowledge of the inhibitory

action of the prior art compounds having been corroborated by testimony and documentary evidence. During the proceedings before the Board, the burden of proof rested upon Cross to show that the Japanese priority application was deficient. 37 C.F.R. §1.257(a). On review, Cross bears the burden of proof to show that the Board erred in finding that the Japanese priority application had adequately disclosed a practical utility. Reviewing the relevant evidence presented to the Board as a whole, we are not persuaded that Cross has met this burden of proof.

[1] The final question we must address is whether the inhibitory activity for thromboxane synthetase in human or bovine platelet microsomes, i.e., an in vitro utility, is sufficient to comply with the practical utility requirement of §101. Based upon the facts of this case, we are not persuaded that the Board erred in finding that the in vitro utility disclosed in the Japanese priority application for the compounds of the count is sufficient to establish a practical utility.

Our predecessor court has noted that adequate proof of any pharmacological activity constitutes a showing of practical utility. See, e.g., Nelson, 626 F.2d at 856, 206 USPQ at 883; Rey-Bellet, 493 F.2d at 1383, 181 USPQ at 454. Dr. Ramwell testified that initial testing of compounds for a particular pharmacological activity is typically done in vitro. In vitro testing permits an investigator to establish the rank order of compounds with respect to the particular pharmacological activity, i.e., to determine the relative potency of the compounds. Compounds having the highest ranking or potency are then selected for further testing in vivo. Presumably this is the accepted practice in the pharmaceutical industry inasmuch as Cross has not proferred any evidence refuting this testimony of Dr. Ramwell, and we note that this practice has an inherent logical persuasiveness. In vitro testing, in general, is relatively less complex, less time consuming, and less expensive than in vivo testing. Moreover, in vitro results with respect to the particular pharmacological activity are generally predictive of in vivo test results, i.e., there is a reasonable correlation therebetween. Were this not so, the testing procedures of the pharmaceutical industry would not be as they are. Iizuka has not urged, and rightly so, that there is an invariable exact correlation between in vitro test results and in vivo test results. Rather, Iizuka's position is that successful in vitro testing for a particular pharmacological activity establishes a significant probability that in vivo testing for this particular pharmacological activity will be successful.

As discussed above, Dr. Ramwell testified that the parent imidazole and 1-methylimidazole compounds had been subjected to both in vitro and in vivo testing as of the critical date, this corroborated by documentary evidence, and found to possess an inhibitory effect for thromboxane synthetase. Based upon this, Dr. Ramwell further testified that he would expect that in vivo testing of the imidazole derivatives of the phantom count would show that these compounds also possessed an inhibitory action for thromboxane synthetase, i.e., there would be a reasonable correlation between in vitro test results and in vivo test results. This evidence was found sufficient by the Board as proof that the Japanese priority application had disclosed a completed practical utility for the imidazole derivatives of the phantom count in inhibiting thromboxane synthetase in human or bovine platelet microsomes. Cf. Rey-Bellet, 493 F.2d at 1386-87, 181 USPQ at 457.

[2] Cross argues that the in vitro utility disclosed by the Japanese priority application is not per se useful, and that more sophisticated in vitro tests, using intact cells, or in vivo tests are necessary to establish a practical utility. [19] Cross is arguing that there must be a rigorous correlation of pharmacological activity between the disclosed in vitro utility and an in vivo utility to establish a practical utility. We, however, find ourselves in agrement with the Board that, based upon the relevant evidence as a whole, there is a reasonable correlation between the disclosed in vitro utility and an in vivo activity, and therefore a rigorous correlation is not necessary where the disclosure of pharmacological activity is reasonable based upon the probative evidence. Cf. Nelson, 626 F.2d at 856, 206 USPQ at 883-83.

Our predecessor court has accepted evidence of in vivo utility as sufficient to establish a practical utility. See, e.g., Nelson v. Bowler, 626 F.2d 853, 206 USPQ 881 (CCPA 1980); In re Jolles, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); Rey-Bellet v. Englehardt, 493 F.2d 1380, 181 USPQ 453 (CCPA 1974).

Opinions of our predecessor court have recognized the fact that pharmacological testing of animals is a screening procedure for testing new drugs for practical utility. See, e.g., In re Jolles, 628 F.2d 1322, 1327, 206 USPQ 885, 890 (CCPA 1980). This in vivo

testing is but an intermediate link in a screening chain which may eventually led to the use of the drug as a therapeutic agent in humans. We perceive no insurmountable difficulty, under appropriate circumstances, in finding that the first link in the screening chain, in vitro testing, may establish a practical utility for the compound in question. Successful in vitro testing will marshal resources and direct the expenditure of effort to further in vivo testing of the most potent compounds, thereby providing an immediate benefit to the public, analogous to the benefit provided by the showing of an in vivo utility. Cf. Nelson, 626 F.2d at 856, 206 USPQ at 883.

Today, under the circumstances of the instant case, where the Japanese priority application discloses an in vitro utility, i.e., the inhibition of thromboxane synthetase in human or bovine platelet microsomes, and where the disclosed in vitro utility is supplemented by the similar in vitro and in vivo pharmacological activity of structurally similar compounds, i.e., the parent imidazole and 1-methylimidazole compounds, we agree with the Board that this in vitro utility is sufficient to comply with the practical utility requirement of §101.

3. Enablement

The Board found that the knowledge as to the use of the pharmacological activity disclosed in the Japanese priority application lay in the fact that the system was a microsome system, microsome systems admittedly being known to those skilled in the art. Employing a microsome assay, the skilled worker could determine the relative strength of the compounds of the count vis-a-vis the known parent imidazole and 1-methylimidazole compounds. Thus, the dosage in the microsome assay milieu could be determined without inventive skill or undue experimentation.

Since we have agreed with the Board that the practical utility for the imidazole derivatives of the phantom count lies in their pharmacological activity in the microsome environment, the how-to-use requirement of §112 must be analyzed with reference to the microsome environment. We are confronted with a disclosure, similar to the situation before the court in Bundy, that fails to reveal dosages for the novel compounds per se. 642 F.2d at 434, 209 USPQ at 51. Although the Japanese priority application does disclose the fact that the imidazole derivatives of the phantom count possess a pharmacological activity similar to the parent imidazole and 1-methylimidazole compounds, the priority application, unlike the application in Bundy, does not disclose dosages for the parent imidazole and 1-methylimidazole compounds.

We agree with the Board, however, that this deficiency in the Japanese priority application is not fatal. The testimonial evidence of Dr. Ramwell, corroborated by certain documentary evidence, showed that those skilled in the art had available, at the critical date, information as to approximate dosage levels for the parent imidazole and 1-methylimidazole compounds to produce an I_{C50} effect, i.e., a 50% inhibition of thromboxane synthetase, in a microsome milieu. The objective of the pharmaceutical research undertaken by the parties was to discover imidazole derivatives having a potent inhibitory effect for thromboxane synthetase. Therefore, we believe it is logical, as did the Board, that the starting point for determining I_{C50} dosage levels for the imidazole derivatives of the phantom count would be the I_{C50} dosage levels of the parent imidazole and 1-methylimidazole compounds. The Board found that there was sufficient credible evidence that one skilled in the art, without the exercise of inventive skill or undue experimentation, could determine the I_{C50} dosage level for the imidazole derivatives of the phantom count in the microsome environment. Cf. Bundy, id., 209 USPQ at 51. We do not believe the Board erred in arriving at this conclusion. This is not a case such as In re Gardner, 427 F.2d 786, 166 USPQ 138 (1970), where the CCPA held that the applicant's disclosure was nonenabling because inventive skill and undue experimentation would be required to discover approprite dosages for humans, i.e., a therapeutic use. In the instant case, we are confronted with a pharmacological activity or practical utility, not a therapeutic use.

While we agree with the Board that the disclosure in the Japanese priority application is somewhat confusing with respect to the 2.5 x 10- 8level of molar concentrations, and that the 2-[p-(1-imidazolylmethyl) phenoxy]-acetic acid hydrochloride compound is outside the phantom count of the interference, this disclosed molar concentration, we believe, does provide some probative value going towards the sufficiency of the Japanese priority application for an enabling disclosure. The disclosed molar concentration would provide sufficient information as to an initial dosage level so that one skilled in the art could determine, without inventive skill or undue experimentation, the necessary molar concentrations for the imidazole derivatives of the phantom cOunt to achieve the desired pharmacological effect, i.e., the 50% inhibition of thromboxane synthetase in human or bovine platelet microsomes.

[3] The Board held the disclosure of the Japanese priority application adequate to satisfy the first paragraph of §112. The burden is on Cross to show Board error in arriving at this conclusion, and we are not persuaded that Cross has successfully carried this burden. Accordingly, we are satisfied that the how-to-use requirement of §112 has been complied with by the disclosures of the Japanese priority application.

Affirmed.

Footnotes

Footnote 1. We note a discrepancy, shown underlined in the above count, between the phantom count as set forth by the primary examiner and that reported by the Board in its decision. The phantom count set forth herein is the one propounded by the primary examiner. However, as will become apparent from the ensuing discussion, the substance of the phantom count is not crucial to resolution of the issues presented by this case.

Footnote 2. The formation of TXA 2in an arachidonic acid challenge is a sequential process initiated by the conversion of arachidonic acid to postaglandin PGG 2by the action of cyclooxygenase, which adds oxygen to the acid. Peroxidase converts the prostaglandin PGG 2to prostaglandin PGH 2, which in turn is converted by thromboxane synthetase to TXA 2.

Footnote 3. Iizuka's position is that, as of the "critical date" of his application, TXA 2was widely accepted in the art as causing platelet aggregation. Cross' position is that, as of the "critical date," platelet aggregation was believed to be nonspecific, i.e., platelet aggregation *may* occur in the presence of thromboxane synthetase, but thromboxane synthetase is not necessary for platelet aggregation. We note in retrospect that THE MERCK INDEX 1345-46 (10th ed. 1983) describes TXA 2as inducing irreversible platelet aggregation. More to the point, however, this court has noted that it is axiomatic that an inventor need not comprehend the scientific principles on which the practical effectiveness of his invention rests, nor is the inventor's theory or belief as to how his invention works a necessary element in the specification to satisfy the enablement requirement of 35 U.S.C. §112. Fromson v. Advance Offset Plate, Inc., 720 F.2d 1565, 1570, 219 USPQ 1137, 1140 (Fed. Cir. 1983).

Footnote 4. Each party relies on the filing date of its foreign priority application to establish a constructive reduction to practice, the earliest date of invention to which each party is entitled under the patent laws of the United States. Kawai v. Metlesics, 480 F.2d 880, 885-86, 178 USPQ 158, 162 (CCPA 1973).

Footnote 5. More specifically, the issue before the Board was whether the Japanese priority application complied with the how-to-use requirement of 35 U.S.C. §112. Section 112 of Title 35 provides, in pertinent part, that:

> The specification shall contain a written description of the invention, of the manner and process of making and *using* it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and *use* the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention. (Emphasis added.)

Should Iizuka's Japanese priority application be found nonenabling with respect to the how-to-use requirement of §112, or otherwise found deficient under the patent laws of the United States, priority would be awarded to Cross based upon his unchallenged entitlement to the benefit of his British application.

Footnote 6. Generally, in vitro refers to an environment outside of a living organism, usually an artificial environment such as a test tube or culture. In contradistinction, in vivo generally refers to an environment within a living organism, such as a plant or animal, or it may refer to a particular portion of an organ external to the living organism, e.g., rat aortic loop.

Footnote 7. Utility is a fact question. Raytheon Co. v. Roper Corp., 724 F.2d 951, 956, 220 USPQ 592, 596 (Fed. Cir. 1983), cert. denied, 105 S. Ct. 127 (1984). Enablement under §112, paragraph 1, i.e., the how-to-use requirement, is a question of law. Id. at 960 n.6, 220 USPQ at 599 n.6.

Footnote 8. While questions one and two are closely connected, a thorough analysis of the utility issue requires first, a determination as to what utility is disclosed, i.e., the stated utility, for the invention claimed in the application. Only after the stated utility has been determined, can a proper analysis be undertaken to determine if the stated utility complies with the "practical utility" requirement of §101. As noted above, these questions regarding utility are factual in nature, see supra note 7, and are to be determined in the first instance by the PTO, the agency with the expertise in this regard.

Footnote 9. In applications prepared in the United States by experienced patent drafters, the drafter of the application typically sets forth objectives for the invention in the "Summary of the Invention" section of the application. These objectives will normally be consonant with the utility disclosed for the invention. As this court has noted, "[w]hen a properly claimed invention meets at least one stated objective, utility under §101 is clearly shown." Raytheon Co. v. Roper Corp., 724 F.2d 951, 958, 220 USPQ 592, 598 (Fed. Cir. 1983), cert. denied, 105 S. Ct. 127 (1984).

Footnote 10. Under the facts of the instant case, utility and enablement questions are ancillary to priority. In the interference proceeding, Cross raised the issue as to whether the Japanese priority application contained sufficient disclosure to satisfy §112. As noted above, see supra note 5, if Cross prevails on this issue the Japanese priority application would be removed as the basis for awarding priority to Iizuka. See generally 37 C.F.R. §§1.225, .231, .258.

Footnote 11. A platelet microsome is an in vitro milieu consisting of blood platelets, the small, colorless corpuscles in the blood of all mammals, and other finely granular elements of protoplasm, such as ribosomes, fragmented endoplasmic reticula and mitochondrial christae.

Footnote 12. Generally, pharmacological activity refers to the properties and reactions of drugs, especially with relation to their therapeutic value.

Footnote 13. For purposes of the present opinion, we consider the phrase "substantial utility," as enunciated in Brenner, to be synonymous with the phrase "practical utility" as used in subsequent opinions of the CCPA.

Footnote 14. We recognize that Nelson dealt with tests which were found adequate to establish an actual reduction to practice, as opposed to a constructive reduction to practice. We agree with the Board that principles applicable to a determination of an actual reduction to practice are generally germane to a constructive reduction to practice.

Footnote 15. Both parties admitted that the GC-SMS test adequately simulated in vivo smooth muscle stimulation.

Footnote 16. The three tests, all in vivo type tests carried out on laboratory animals, were: (1) the Mental Health General Screening Test which indicated the physical response, or absence of a response, of test animals to a drug, indicating the presence, or absence, of a desired pharmacological activity; (2) the Tetrabenazine Antagonism Test which screened drugs for antidepressant activity; and (3) the Sidman Avoidance Test which screened drugs for tranquilizing activity.

Footnote 17. Contrary to Cross' contention in the Reply Brief, the evidence of record relied upon by Cross to show significant structural dissimilarity appears to us to be directed to the fact that there is a wide disparity in potency for thromboxane synthetase inhibition between the parent imidazole compound and prior art imidazole derivatives. Cross has not directed our attention to any specific evidence of record which establishes, or tends to establish, significant structural dissimilarities between the basic imidazole compound and the imidazole derivatives of the phantom count. Variation in potency, moreover, is a matter of degree of activity, see Bundy, 642 F.2d at 433, 209 USPQ at 51, but is still indicative of activity. There is no requirement that the compounds have the same degree of activity. Id., 209 USPQ at 51. Moreover, this argument may be construed as a tacit admission that the parent imidazole compound does possess the particular pharmacological activity of inhibiting thromboxane synthetase.

Along this line, we note that Dr. Smith, Cross' expert witness, testified generally, based upon the exhibits proffered by Iizuka, see infra note 18, that the parent imidazole compound possessed pharmacological activity for inhibiting thromboxane synthetase, although stating that there was a wide potency spectrum for prior art imidazole derivatives with respect to the parent imidazole compound.

Cross has directed the court's attention to the fact that the Japanese priority application, while disclosing that the parent imidazole and 1-methylimidazole compounds possess an inhibitory action for thromboxane synthetase, further discloses that this inhibitory effect is not satisfactory and that the parent imidazole and 1-methylimidazole compounds have not been put to practical therapeutic use. But a therapeutical utility is not necessarily synonymous to a pharmacological activity. Cf. Nelson, 626 F.2d at 856, 206 USPQ at 883.

Footnote 18. For example, Table I in the article "Imidazole: A Selective Inhibitor of Thromboxane Synthetase," PROSTAGLANDINS, Vol. 13, No. 4, April 1977 (Iizuka Exhibit No. 6), lists 1-methylimidazole and the parent imidazole compounds as possessing inhibitory activity for thromboxane synthetase, thereby offering corroboration of Dr. Ramwell's testimony.

The Board noted that Iizuka Exhibits 2-6 and 10-12, while inadmissible for the purpose of establishing the truth of what they say on their face, are admissible to bolster and support the testimony of Dr. Ramwell, as well as for the purpose of establishing what literature was available to the art at the critical time. Thus, for review purposes, we have examined these exhibits for their corroborating value with respect to Dr. Ramwell's testimony.

Footnote 19. Cross is seemingly arguing that the in vitro disclosure of the Japanese priority application is only a potential utility. See Knapp v. Anderson, 477 F.2d 588, 591, 177 USPQ 688, 691 (CCPA 1973).

- End of Case -

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